Impact of Gestational Age on Neuroprotective Function of Placenta-Derived Mesenchymal Stromal Cells.

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Public Summary:
Myelomeningocele (MMC), the most severe form of spina bifida, results from incomplete closure of the spinal canal during development, causing impaired lower extremity, bladder and bowel function. Though results of The Management of Myelomeningocele Study (MOMS) clinical trial demonstrated in utero repair of MMC improved motor movement in children compared to children treated after birth, many were still unable to walk. Early results from our study testing the effect of an in utero repair with placental derived mesenchymal stem/stromal cells (PMSCs) further improved walking outcomes compared to the standard in utero repair method used in the MOMS trial. The ability of PMSCs to differentiate into many cell types and release proteins that can protect neurons that promote localized tissue and cell regeneration has been used to treat a variety of diseases. However, the ability of PMSCs of all gestational ages to protect neurons has not been evaluated previously. PMSCs were isolated from the first trimester, second trimester, and third trimester placentas. Secretion of two proteins important for cellular survival and growth, brain derived neurotrophic factor and hepatocyte (liver cell) growth factor, were evaluated. Secretion of cytokines responsible for regulating the immune system and protecting neurons were also evaluated. All cell lines from each gestational age secreted both neuron protection factors and cytokines, and multiple cell lines from each gestational age exhibited neuron protection properties. These results indicate the donor pool for PMSCs may be greater than originally excepted, and further studies are needed to evaluate more subtle differences in cell function at different gestational ages.

Scientific Abstract:
INTRODUCTION: The Management of Myelomeningocele Study demonstrated that in utero repair of myelomeningocele improved motor outcomes compared with postnatal repair. However, even after in utero repair, many children were still unable to walk. We have previously demonstrated that augmentation of in utero repair with early-gestation placental mesenchymal stromal cells (PMSCs) improves motor outcomes in lambs compared with standard in utero repair. The neuroprotective potential of PMSCs of all gestational ages has not been evaluated previously. METHODS: PMSCs were isolated from discarded first trimester (n = 3), second trimester (n = 3), and term (n = 3) placentas by explant culture. Cytokine array analysis was performed. Secretion of two neurotrophic factors, brain-derived neurotrophic factor and hepatocyte growth factor, was evaluated by enzyme-linked immunosorbent assay. An in vitro neuroprotective assay demonstrated to be associated with in vivo function was performed. RESULTS: All cell lines secreted immunomodulatory and neuroprotective cytokines and secreted the neurotrophic factors evaluated. Increased neuroprotective capabilities relative to no PMSCs were demonstrated in two of the three first trimester cell lines (5.61, 4.96-6.85, $P < 0.0001$ and 2.67, 1.67-4.12, $P = 0.0046$), two of the three second trimester cell lines (2.82, 2.45-3.43, $P = 0.0004$ and 3.25, 2.62-3.93, $P < 0.0001$), and two of the three term cell lines (2.72, 2.32-2.92, $P = 0.0033$ and 2.57, 1.41-4.42, $P = 0.0055$). CONCLUSIONS: We demonstrated variation in neuroprotective function between cell lines and found that some cell lines from each trimester had neuroprotective properties. This potentially expands the donor pool of PMSCs for clinical use. Further in-depth studies are needed to understand potential subtle differences in cell function at different gestational ages.